THE PATHOGENESIS AND TREATMENT OF THE MEGALOBlastic ANAEMIAS *

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Even a superficial examination of the subject will reveal the vast amount of interesting and original research which has already taken place on the megaloblastic anaemias. This work is far from finished and almost every year some new discovery is made for the treatment of this group of anaemias. Through the mass of work already done certain guiding principles stand out.

First of all I would place Minot's discovery in 1926 that Addison's Anaemia could be cured by liver. Secondly, Arinkin's description in 1929 of sternal puncture marrow biopsy set free the clinical observer from the restraints imposed by the dead hand of the morbid anatomist. The gain here was twofold, first, serial marrow biopsies could be performed with little inconvenience to the patient and, secondly, by causing much interest to be placed on cellular instead of architectural pathology many obscure points of marrow cell maturation were rapidly cleared up. The third fundamental point, the nature of the red cell changes in these anaemias, was clarified by the meticulous observations of Price-Jones; observations which were so overwhelmingly studied by him that this valuable haematological method has been little used because of the labour allegedly involved. It is not fully understood that simplified techniques of red cell diameter measurement such as that described by Belyavin and myself (Humble and Belyavin 1947) give much valuable information unobtainable by other methods and the results can be obtained in the same time as it takes to perform a mean cell volume determination. It is not necessary, as is so frequently stated, to measure as many as 500 red cells; 100 to 250 cells are quite enough for clinical purposes as the standard error of the Mean Cell Diameter is inversely proportional to the square root of the number of cells measured.

In a subject where so little is known as to aetiology where treatment is only now becoming

clarified, the importance of accurate diagnosis stands supreme.

The diagnosis and treatment of an uncomplicated case of Addison's Anaemia presents little difficulty if specific therapy is withheld until the cardinal points of diagnosis have been established. These points are: (1) The history and clinical findings. (2) A megalocytic anaemia with increase of red cell diameter and volume, and a normal haemoglobin saturation. (There is also usually leucopenia and a 'shift to the right' of the neutrophils.) (3) A megaloblastic marrow in the absence of previous treatment. (4) Histamine fast achlorhydria. Then treatment by a potent liver extract or its equivalent should produce a good reticulocyte response with a satisfactory rise in haemoglobin and red cells.

Unfortunately cases are commonly seen where a casual injection of liver extract has been given previously which has shifted the marrow and blood picture towards the normal. Treatment before diagnosis and 'blunderbuss' therapy offend all canons of common sense.

The diagnosis and treatment of the other forms of megaloblastic anaemias, e.g. those accompanying steatorrhea, carcinoma ventriculi, diphylobothrium latum infestation or the so-called pernicious anaemia of pregnancy require care and judgment. These cases often show evidence of lack of absorption of other haematinic substances so that the anaemia is not typical. HCl is often present in the gastric juice. Nevertheless diagnosis must be accurate if treatment is to be correct. The following cases have been selected to illustrate these points.

Case 1

Addison's Anaemia with accompanying iron deficiency. This female patient, aged 52 years, spoke no English. She had fever up to 103° F. to 104° F. at night, marked jaundice and splenomegaly. There was a loud systolic apical murmur. A blood count showed haemoglobin 49 per cent. (Haldane) red blood cells 1,600,000 per cu.mm. Packed cell volume (P.C.V.) 19 per cent. Mean

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FIG. 1.—Price Jones curve to show anisocytosis with low M.C.D. (Case 1).

FIG. 2.—Progress of Case 1 showing Fe deficiency unmasked by liver treatment.

FIG. 3.—Progress of Case 2.

FIG. 4.—Progress of Case 3.

FIG. 5.—Progress of Case 5.

FIG. 6.—Price Jones curve of Case 6 showing the anisocytosis.

In FIGS. 2, 3, 4, 6 and 8 Haemoglobin is represented by solid line ; Red blood cells by dotted line ; Reticulocytes by dotted and dashed line.

corpuscular volume (M.C.V.) 118 cu. μ . Mean corpuscular haemoglobin concentration per cent. (M.C.H.C. per cent.) 33 per cent. The slide showed marked anisocytosis. Mean corpuscular diameter (M.C.D.)—7.79 μ . Standard deviation—0.85 μ (Fig. 1). The marrow was megaloblastic. She was treated with liver extract and responded well (Fig. 2). When the haemoglobin was 75 per cent. approximately her condition remained stationary and the addition of iron was needed to complete the remission.

Case 2

Addison's Anaemia complicated by chronic nephritis and other diseases. This was a female patient aged 42 years when first seen in June 1945. She gave two weeks' history of weakness and oedema of the legs. She was very pale and had a smooth tongue. The oedema subsided on bed rest. Haemoglobin 28 per cent. Red blood cells 1,400,000 per cu. mm. P.C.V. 13 per cent. M.C.V. 93 cu. μ . M.C.H.C. per cent. 31 per cent. The film showed anisocytosis with no obvious macrocytosis. There was histamine fast achlorhydria. The marrow was megaloblastic. A diagnosis of Addison's Anaemia with iron deficiency was made. Treatment with liver extract and ferrous sulphate was begun. Four days later, massive oedema and albuminuria was found and an Ellis type 2 nephritis was diagnosed. Nine days after therapy began—haemoglobin 40 per cent., reticulocytes 8.4 per cent. After 22 days' treatment—haemoglobin 52 per cent., red blood cells 2,850,000 per cu. mm. P.C.V. 27 per cent. One week later serum albumin 2.32 per cent., serum globulin 2.3 per cent. Total serum proteins 4.62 per cent. The urine contained much albumin and a severe *Esch. Coli urinary infection* was also found. The haemoglobin remained stationary (Fig. 3) and two pints of blood, followed later by two pints of packed red cells, were given. At a later date a further two pints of packed cells were given.

She was then discharged from hospital, in November 1945, haemoglobin 85 per cent., no oedema. She was well until June 1946, except for an *abscess of the buttock* (*Staphylococcus Aureus*), and a recrudescence of the *urinary infection*. The nephritis and oedema then recurred and on February 1, 1947, the haemoglobin was 85 per cent., R.B.C. 3,790,000 per cu. mm., M.C.D. 7.8. Folic acid (10 mg.b.d.) was given and in nine days a dramatic rise of Hgb. to 100 per cent. and a reticulosis of 7 per cent. was seen. The blood has been normal since on liver and folic acid therapy despite a typical attack of *infective hepatitis* lasting 10 days in 1947, and an attack of *spasmodic asthma* controlled by ephedrine in March 1949.

On March 6, 1950, she was well, free from oedema. B.P. 120/60, Hgb. 114 per cent., R.B.C. 5,620,000 per cu.mm. The treatment at present is Hepaloid 4 cc. a month. Folic acid 5 mg. b.d.

Case 3

Addison's Anaemia with sub-acute combined degeneration of the spinal cord. This case showed no response to injected liver but a good response to Vitamin B₁₂ (Glaxo).

Case History

A man of 70. There was a typical history of sub-acute combined degeneration of 8 to 12 weeks standing. The principal complaint was numbness and paresthesiae and anaesthesia affecting the hands and feet. The Hgb. was 72 per cent., R.B.C. 3,010,000 per cu.mm., P.C.V. 34 per cent. M.C.V. 113 cu. μ , M.C.H.C. per cent. 29 per cent. A fractional test meal showed achlorhydria. He was treated energetically with liver for 10 days, but showed no reticulocyte response. He was then treated with Vitamin B₁₂ (Fig. 4). He made a small reticulocyte response and a steady rise of Hgb., and R.B.C. The sensory changes in his hands and feet somewhat improved but he has not yet obtained normal sensation in his fingers.

Case 4

Carcinoma of the stomach with megaloblastic anaemia. This case was not well handled, as the condition was not fully investigated at the onset.

This was a man of 48. He complained of dyspnoea, tiredness and dyspepsia in February 1943. He was sent by his own doctor to a pathologist who diagnosed a macrocytic anaemia and carcinoma of the stomach. The Hgb. was 65 per cent., R.B.C. 1,200,000 per cu.mm. His doctor gave him one injection of liver in March and one in April. He was then sent to Westminster Hospital as having a ? lesion of the stomach. A barium meal revealed carcinoma of the stomach. The Hgb. was 82 per cent. and the red blood cells were 4,600,000 per cu.mm. A fractional test meal showed a foul resting juice containing blood. No HCl present. The stomach and transverse colon were resected in June as a palliative operation. There were no metastases in the liver. The lesion found was a carcinoma of the stomach originating apparently in the lesser curvature. Many malignant glands were found. He recovered well from the operation but on August 26, 1943, the Hgb. was 48 per cent. and the R.B.C. were 2,080,000 per cu.mm. The bone marrow was megaloblastic. He was given liver and responded well having a reticulocytosis of 16 per cent. at seven days after treatment was commenced. On this day a secondary nodule

FIG. 7.—Progress of Case 6.

FIG. 8.—Price Jones Curves of Case 7 showing change of cell diameters after expulsion of parasite.

FIG. 9.—Progress of Case 7.

FIG. 10.—Price Jones curves of Case 8. Note 'shift to the right' of M.C.D. following aminopterin therapy.

was found in the abdominal wall. In October the Hgb. was 102 per cent., R.B.C. 4,950,000 per cu.mm. He died in December 1943 of generalized multiple metastases.

It is not clear whether this is a case of carcinoma of stomach with secondary megaloblastic anaemia or Addison's Anaemia with carcinoma of the stomach supervening. In favour of the first theory is that his two brothers were alleged to have duodenal ulcers, so that familial achlorhydria can hardly have existed.

Case 5

Megaloblastic anaemia with steatorrhoea showing response to folic acid after failure of response to injected liver extract.

This was a man of 51. He had suffered from eczema since 1930 and had been treated by two weeks' sodium amylal sedation for this complaint one month before his anaemia became manifest. He had diarrhoea with clay-coloured stools on and off for a year. He was a thin hypochondriacal man. The tongue was smooth. The Hgb. was 46 per cent., R.B.C. 1,850,000 per cu.mm., P.C.V. 22 per cent., M.C.V. 114 cu.microns, M.C.H.C. per cent. 31.4 per cent. The marrow was megaloblastic. The fractional test meal was normal. There was steatorrhoea, total faecal fat 39.0 gm. per cent., split fat 28.7 gm. per cent., unsplit fat 10.3 gm. per cent. (38 per cent. of the total). Liver therapy was begun but a sudden fall of Hgb. to 28 per cent. necessitated transfusion. Folic

acid 10 gm. b.d. were then given (see Fig. 5) and a steady rise of Hgb. followed but no great reticulosis could be demonstrated. He is now well.

Case 6

'Multiple Deficiency' Anaemia with multiple reticulocyte response to therapy. The patient, an Irishwoman, aged 55, had worked in England in a laundry for six months. She complained of loss of energy and of feeling very cold. She did not appear to be a very reliable witness. She was pale and sallow, the tongue was smooth and the tip red. The liver and spleen were palpable. The Hgb. was 23 per cent., the R.B.C. were 1,300,000 per cu.mm., P.C.V. 13 per cent., M.C.V. 100 cu. microns, M.C.H.C. per cent. 26 per cent., M.C.D. 7.37 microns. Standard deviation—1.059 microns (Fig. 6). The film shows gross anisocytosis. The fractional test meal was normal and a barium meal showed a duodenal ulcer (this was apparently symptomless). She was given liver and iron, followed by ascorbic and folic acid and responded by three reticulocyte responses (Fig. 7). She is now well.

Case 7

Diphyllobothrium latum anaemia. This case will, it is hoped, be reported more fully elsewhere. (Harland, Humble, and Mann, 1950.) It is shown because a diagnosis of Addison's Anaemia was made elsewhere although the patient was aged 22 and was a Finn. Clinically, little found. There was histamine fast achlorhydria. The marrow was megaloblastic but not obviously typical. (Liver had been given one month previously.) Haemoglobin 60 per cent., red blood cells 2,500,000 per cu.mm., P.C.V. 30 per cent.,

M.C.V. 120 cu. microns, M.C.D. 8.34 microns. Standard deviation 0.9 microns (Curve A, Fig. 8). Ova of diphyllobothrium latum were found repeatedly in the stools. A vermifuge produced two worms and this was followed by a reticulocytosis with rise of haemoglobin and red blood cells (Fig. 9) and return of red cell size to normal (Curve B, Fig. 8).

Case 8

Production of megaloblastic anaemia by antifolic acid compounds (aminopterin). This was in a male aged 31 seen in September 1949. There were glands in the neck at first, then axillary glands, then hepatosplenomegaly with haemorrhages from the nose, urinary tract and bowel. He was diagnosed as acute lymphatic leukaemia. The Hgb. was then 42 per cent. and the red blood cells 2,250,000 per cu.mm., M.C.D. 7.05 microns (Fig. 10, Curve A). Aminopterin (Amino-pteroyl glutamic acid) was administered and after 10 mg. had been given a distinct macrocytosis appeared in the blood (Fig. 10, Curve B). A few days later megaloblasts were found in the peripheral blood.

These cases show that megaloblastic anaemia are not infrequently complicated by other deficiencies, and present with a variety of causes. An abnormal mental pattern has been found frequently in our cases and this may perhaps have aided the anaemia to become established by developing curious dietary habits. It is an interesting feature and should be the subject of more study.

In conclusion I would like to thank the staff of Westminster Hospital for permission to quote from their records, and the Department of Medical Photography for making the diagrams.

BIBLIOGRAPHY

- HARLAND, J. C., HUMBLE, J. G., and MANN, P. G. (1950), *Brit. Med. J.*, ii, 188.
HUMBLE, J. G., and BELYAVIN, G. (1948), *J. Clin. Path.*, i, 77.

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